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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,937	05/30/2001	Bin Wu	PP-01623.002	8716

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,937	WU ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-21 and 23-26* is/are pending in the application.

4a) Of the above claim(s) *6-19* is/are withdrawn from consideration.

5)☒ Claim(s) *5* is/are allowed.

6)☒ Claim(s) *1,3,4,20,21 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 24, 2004 has been entered.

Receipt is acknowledged of a reply to the previous Office Action, filed June 23, 2004. Amendments were made to the claims.

Claims 1, 3-21 and 23-26 are pending in the instant application. Claims 6-19 have been withdrawn from consideration as being drawn to a non-elected invention. Any rejection of record in the previous Office Action, mailed December 24, 2003, that is not addressed in this action has been withdrawn.

Applicant's request to transfer the instant Application from the current Art Unit 1636 to Art Unit 1635 is acknowledged. Unfortunately, at the current time it is not possible to transfer the application. However, in order to satisfy Applicant's concerns regarding an examination commensurate with the practice of Art Unit 1635, the instant Office Action will be reviewed by a Primary Examiner from Art Unit 1635.

Information Disclosure Statement

The information disclosure statement filed March 24, 2004 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to the Office Action for Applicant's records.

Specification

The disclosure is objected to because of the following informalities: it is noted that on page 6, lines 14 and 16, Applicant refers to Figures 2A-B and Figures 3 and 4; however, it is noted that the instant specification only contains a single figure and corresponding description, Figure 1.

Appropriate correction is required.

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 21 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for the reasons set forth in the previous Office Action**.

It is noted that these claims remain rejected under 35 USC § 112, first paragraph because the claims recite the limitation "therapeutically effective amount." This limitation represents functional language that requires the product to be enabled for a therapeutic use, thus the claims remain rejected as not being enabled for a therapeutic use.

Response to Arguments Concerning Claim Rejections - 35 USC § 112, First Paragraph

Applicant's arguments filed March 24, 2004 have been fully considered but they are not persuasive. It is noted that there are several arguments regarding the identification of antisense molecules that will specifically target and inhibit the expression of KIAA0175; these arguments will not be addressed further because the rejection is no longer maintained with respect to this aspect of the invention. The following grounds of traversal are presented as it relates to the enablement rejection as maintained in view of the functional language ("therapeutically effective amount") set forth in the claims:

1. It is argued that the instant specification is not at odds with the state of the prior art because the Branch reference clearly indicates that the relationship between *in vitro* and *in vivo* activity is an active area of research (see for example pages 10-11, bridging paragraph of Applicant's response). Furthermore, the Office's characterization of antisense technology as "problematic" is traversed as inaccurate because the Branch reference (used in support of the characterization) indicates that the field is a "diamond mine" (see for example pages 11-12, bridging paragraph of Applicant's response).

2. It is argued that antisense oligonucleotides have numerous utilities (original emphasis), including *in vitro* inhibition of KIAA0175 to test the cytotoxicity of radiation and

chemotherapeutic agents in the presence and absence of the KAA0175 gene product (see for example page 12, second full paragraph of Applicant's response). It is further asserted that the Office has inappropriately focused on the therapeutic utility of the instantly claimed invention, ignoring these other possibilities (see for example page 12, bottom paragraph of Applicant's response). It is finally urged that the instant invention is much broader in scope than a therapeutic use for the claimed invention (see for example page 13, second full paragraph of Applicant's response).

3. It is argued that the generic problems that pertain to the therapeutic use of antisense oligonucleotides (such as delivery and sustained expression of the nucleic acid) "are not addressed by, nor are they intended to be addressed by, the current invention" (see for example page 14, first paragraph of Applicant's response).

Applicant's arguments have been considered but are not found convincing for the following reasons:

1. First, the enablement rejection regarding a therapeutic use of the claimed antisense oligonucleotides is not a question of whether or not the instant specification and the state of the art are at odds, *per se*; rather it is a question of whether or not the teachings in the state of the art and the instant specification are sufficient to allow the skilled artisan to make and use the claimed invention. Branch clearly indicates that the relationship between the *in vitro* and *in vivo* use of antisense oligonucleotides is under research; thus, the skilled artisan would understand that there is a great deal of empirical experimentation required to correlate *in vitro* cell culture results to *in vivo* therapeutic treatments. In the instant case, Applicant simply provides *in vitro* cell culture inhibition of KIAA0175 expression using antisense oligonucleotides, and provides

no correlation between these results and *in vivo* therapy. However, Applicant cannot shield themselves from enabling the *in vivo* use of antisense oligonucleotides simply because the state of the art has not enabled it, and argue that an enabling disclosure would not be expected upon considering the state of the art. Indeed, it is because antisense technology is undergoing continued research concerning this *in vitro/in vivo* relationship that fosters the element of unpredictability leading to a lack of enablement. Second, while Applicant is correct in indicating that Branch characterizes antisense technology as containing "diamond mines," they neglect to point out that in the same breath, Branch characterizes antisense technology as "quicksand" (see page 45 of Branch, as indicated by Applicant in their response). One cannot reasonably ascertain when an antisense oligonucleotide will be a diamond mine, and when one will be quicksand; this is the essence of unpredictability.

2. The instantly rejected claims recite functional language ("therapeutically effective amount") that requires a therapeutic use for the claimed antisense oligonucleotide. Thus, the composition claims must be enabled for therapeutically decreasing the expression of KIAA0175 to enhance the cytotoxic effects of radiation and chemotherapeutic agents. However, as set forth in previous Office Actions and in the response to Applicant's arguments below, the specification is not enabled for a therapeutic use of the claimed invention. Therefore, the claims reciting the functional language "therapeutically effective amount" remain rejected for lacking enablement for a therapeutic use of the claimed composition.

3. The generic problems with respect to the delivery and sustained expression of nucleic acids are at the heart of the enablement rejection. Without a predictable means to deliver the antisense nucleic acids (generally in the form of a vector; see for instance the instant specification, pages

28-34), the skilled artisan cannot use the invention for a therapeutic purpose. Thus, the absence of a teaching (intended or otherwise) in the specification or the state of the art on how to deliver and maintain the expression of an antisense oligonucleotide (at the time of filing) prohibits the skilled artisan from using the instantly claimed invention. As set forth in Applicant's arguments, it is not the intention of the instant invention to address these issues, as it is believed the state of the art adequately teaches the skilled artisan how to use the claimed invention. However, the state of the art is replete with teachings that the delivery and expression of nucleic acids to cells *in vivo* is unpredictable. In the original enablement rejection, the Mountain reference (*TBTECH* **18**:119-128, 2000; see previous Office Actions) was provided to support the position of the Office. To further support the conclusion that the state of the art indicates the unpredictability of delivering and sustaining the expression of a nucleic acid in vivo, the Office now provides additional references that reach the same conclusion as the Mountain reference. Anderson (*Nature* **392**: 25-30, 1998; see entire document) teaches that the problems facing the development of retroviral vectors include efficient delivery and sustained expression of the therapeutic nucleic acid (see for example page 25, right column, first full paragraph), and that problems facing adenoviral vectors include immunogenicity and stable expression of the therapeutic nucleic acid (see for example page 28, left column, first paragraph). Verma *et al.* (*Nature* **389**: 239-242, 1997; see entire document) teaches that the Achilles heel of nucleic acid based therapies is the inability to efficiently deliver and sustain the expression of the therapeutic nucleic acid (see for example page 239, right column, first full paragraph). Thus, the skilled artisan would still be left to overcome these logistical problems with antisense-based therapies in order to practice the claimed invention. Since these problems have yet to be resolved many

years later, this is considered to require an undue and unpredictable amount of trial and error experimentation before the skilled artisan can use the invention for its asserted utility.

In conclusion, the instantly rejected claims recite functional language ("therapeutically effective amount") that requires the claimed product to be enabled for a therapeutic use. However, such a therapeutic invention is highly unpredictable in view of the state of the art and the instant specification. The state of the art indicates the difficulties encountered with (a) delivering the therapeutic nucleic acid to a target cell and (b) sustaining the expression of the nucleic acid in a therapeutically effective amount, and Applicant clearly indicates in their arguments that the instant specification makes no attempt and has no intention of addressing these defects (again, see page 14, first paragraph of Applicant's response). Thus, in view of the unpredictability concerning the instant invention as it regards its asserted utility, the invention is still considered to lack enablement.

NEW REJECTIONS

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the term "or inhibitor thereof." It is unclear if this term refers to the inhibitor of KIAA0175, as set forth in independent claim 1, or if the term refers to an inhibitor of

the antisense molecule that is an inhibitor of KIAA0175 (i.e., an inhibitor of the inhibitor). The indefiniteness stems from the fact that the teachings of the specification refer to an antisense inhibitor of KIAA0175, but do not refer to an inhibitor of that antisense inhibitor. It is further noted that the claims as originally presented were drawn to KIAA015 inhibitors that were not antisense molecules; thus the term "or inhibitor thereof" may be a remnant referring to those additional non-antisense inhibitors, and may thus be misplaced. Finally, the term is indefinite because it is unclear how both the antisense molecule and (putatively) the inhibitor of the antisense molecule can both comprise "at least 17 consecutive nucleotides of the sequence of SEQ ID NO: 9." In other words, it is unclear how an inhibitor and the antisense molecule it inhibits can have the same nucleic acid sequence.

Claim 3 recites the limitation " inhibitor thereof " in reference to claim 1, drawn to an antisense molecule. There is insufficient antecedent basis for this limitation in the claim because the independent claim is drawn to an antisense molecule, and does not include a reference to an inhibitor of an antisense molecule.

Claims 4, 23 and 24 are indefinite for reciting the term "complement thereof" when referring to an antisense molecule, whereby both the antisense molecule and the complement thereof hybridize under stringent conditions to the same molecule, SEQ ID NO: 9. It is unclear how both the antisense molecule and its complement can hybridize to the same molecule. It is further unclear if the term complement thereof is actually intended to refer to the antisense molecule or to SEQ ID NO: 9, especially in light of the instant specification which provides no teaching for using a complement to an antisense oligonucleotide.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The instant rejection is predicated on the following interpretation of the claims. In claim 1, there is no specific indication of a sequence for KIAA0175. Although the instant specification describes one sequence for KIAA0175 (SEQ ID NO: 9), it is unclear if the term KIAA0175 includes other sequences that are not SEQ ID NO: 9 (such as orthologues/homologues). As such, a sequence with significant homology to SEQ ID NO: 9, specifically, may hybridize to an orthologue or homologue of KIAA0175 with 100% correspondence. Furthermore, it is noted

that claims 3 and 23 (and their dependent claims) refer to an antisense molecule that comprises a sequence of SEQ ID NO: 9. Given that SEQ ID NO: 9 represents the gene to be inhibited, one would expect the antisense molecule to hybridize to SEQ ID NO: 9, rather than to comprise SEQ ID NO: 9. Thus, for purposes of applying art, claims 3 and 23 (and their dependent claims) are interpreted as reading "wherein said antisense molecule (or the complement/inhibitor thereof) hybridizes to at least 17 consecutive nucleic acids of the sequence of SEQ ID NO: 9."

Claims 1, 3, 4, 20, 23 and 24 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US 5,700,637 (see entire document; henceforth Southern).

The claims of the above invention are drawn to antisense compounds of either an indeterminate number (claim 1), at least 17 (claims 3, 4) or no more than 25 (claims 20, 23 and 24) nucleotides in length that specifically hybridizes with and inhibits the expression of the KIAA0175 gene, specifically represented by SEQ ID NO: 9 in some claims.

SEQ ID NO: 56 disclosed in Southern (see for example TABLE 1, column 15) is 17 nucleotides in length and possesses 83% identity with a sequence that would specifically hybridize to residues 481-497 of SEQ ID NO: 9 of the instant application. Absent evidence to the contrary, SEQ ID NO: 56 would also hybridize to SEQ ID NO: 9 given the high degree of similarity between the sequences. Although Southern does not specifically teach the function of inhibiting Applicant's instant SEQ ID NO: 9 as claimed in the present application, the above-listed compound of the prior art meets all the structural limitations as set forth in the instant claims. Because the sequence is substantially identical to Applicant's claimed compounds, in the absence of evidence to the contrary the compound of the prior art is thus considered to possess

the functional limitations of specifically hybridizing with and inhibiting the expression of Applicant's instant SEQ ID NO: 9.

Claims 1, 3, 4, 20, 23 and 24 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US 6,087,485 (see entire document; henceforth Brooks-Wilson).

The claims of the above invention are drawn to antisense compounds of either an indeterminate number (claim 1), at least 17 (claims 3, 4) or no more than 25 (claims 20, 23 and 24) nucleotides in length that specifically hybridizes with and inhibits the expression of the KIAA0175 gene, specifically represented by SEQ ID NO: 9 in some claims.

SEQ ID NO: 233 disclosed in Brooks-Wilson (see for example TABLE 1, column 15) is 25 nucleotides long and possesses 88% identity with a sequence that would specifically hybridize to residues 1579-1603 of SEQ ID NO: 9 of the instant application. Absent evidence to the contrary, SEQ ID NO: 233 would also hybridize to SEQ ID NO: 9 given the high degree of similarity between the sequences. Although Southern does not specifically teach the function of inhibiting Applicant's instant SEQ ID NO: 9 as claimed in the present application, the above-listed compound of the prior art meets all the structural limitations as set forth in the instant claims. Because the sequence is substantially identical to Applicant's claimed compounds, in the absence of evidence to the contrary the compound of the prior art is thus considered to possess the functional limitations of specifically hybridizing with and inhibiting the expression of Applicant's instant SEQ ID NO: 9.

Support for these conclusions is drawn from MPEP 2112:

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection**. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

In rejecting the claims of the above under 35 U.S.C. 102 and 103, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed compounds are not anticipated by the compound of the prior art as stated lies with the applicant, as per MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Thus, in the absence of evidence to the contrary, the antisense compounds of claims 1, 3, 4, 20, 23 and 24 of the instant application are considered anticipated and/or obvious as outlined above.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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